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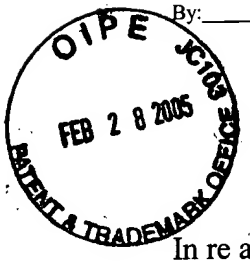
On February 24, 2005

TOWNSEND and TOWNSEND and CREW LLP

By: [signature]

PATENT
Attorney Docket No.: 018512-006610US



IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:

Wickenden et al.

Application No.: 09/939,230

Filed: August 24, 2001

For: METHODS FOR TREATING OR PREVENTING PAIN AND ANXIETY

Customer No.: 20350

Examiner: Jones, Dwayne C.

Technology Center/Art Unit: 1614

DECLARATION OF DR. ALAN WICKENDEN UNDER 37 CFR § 1.132

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

1. I, Alan D. Wickenden, being duly warned that willful false statements and the like are punishable by fine or imprisonment or both (18 U.S.C. § 1001), and may jeopardize the validity of the patent application or any patent issuing thereon, state and declare as follows:

2. All statements herein made of my own knowledge are true, and statements made on information or belief are believed to be true and correct.

3. I am currently employed by Icagen Inc. as a Group Leader of Electrophysiology. I received a Ph.D. in Physiology in 1995 from the University of Birmingham in the United Kingdom. I received a B. Sc. in Pharmacology and Physiology in 1986 from University of Manchester in the United Kingdom. I have conducted research in the field of pharmaceutical drug discovery for approximately 15 years.

4. I am familiar with the subject matter contained in the above-referenced patent application, "METHODS FOR TREATING OR PREVENTING PAIN AND ANXIETY."

5. I have read and I understand the Office Action mailed by the Examiner on August 25, 2004.

6. I understand that claims 450-48, 54-59, 61-65, 70, 71, and 72 are rejected under 35 U.S.C. § 103, as allegedly obvious over Gaster, US Patent 6,235,758 (hereafter referred to as "Gaster").

7. This declaration demonstrates that Gaster fails to teach or suggest a method of treating anxiety by administering KCNQ potassium channel openers. The Examiner asserts that Applicants' invention merely elucidates a mechanistic step that is inherent in the administration of the aryl carbamoyl compounds of Gaster. The Examiner reasons that because this mechanistic step is inherent in the aryl carbamoyl compounds of Gaster, it would have been obvious for one skilled in the art to treat anxiety as claimed.

8. The Examiner asserts that the aryl carbamoyl compounds of Gaster are used to treat anxiety and, therefore, inherently increase ion flow through KCNQ potassium channels. See page 13, line 13 of Examiner's Office Action mailed August 25, 2004. Applicants respectfully disagree with the Examiner's assertion that the aryl carbamoyl compounds of Gaster inherently increase ion flow through KCNQ potassium channels. Applicants respectfully note that it is likely anxiety is caused by multiple mechanisms in addition to increasing ion flow through KCNQ potassium channels. Therefore, some compounds that are used to treat anxiety, including currently marketed medications, do not act as KCNQ openers.

9. Gaster provides no evidence that the disclosed aryl carbamoyl compounds actually reduce anxiety, much less through increasing ion flow through KCNQ potassium channels. Rather, Gaster merely discloses that "certain compounds of the invention exhibit $5HT_{2B}$ antagonist activity." See column 1, lines 20-21. Assuming, arguendo, that the disclosed aryl carbamoyl compounds are capable of reducing anxiety, Applicants submit that there is no basis in fact and/or technical reasoning to reasonably support the determination that the aryl carbamoyl compounds ***necessarily*** increase ion flow through KCNQ potassium channels. Anxiety is a complex disease, like cancer, high blood pressure, heart disease, and depression. Applicants respectfully note that as a complex disease, it is likely that anxiety can be treated by therapeutic agents acting via different biochemical mechanisms, just as cancer, high blood pressure, heart disease, and depression are treated with medicines having different mechanisms and effects. Therefore, not all methods of reducing anxiety would be expected to work by increasing ion flow through a KCNQ potassium channel.

10. $5HT_{2C}$ receptor antagonism is the only reported activity for the aryl carbamoyl compounds of Gaster. One skilled in the art would immediately recognize that $5HT_{2c}$ receptors radically differ in structure and function from KCNQ potassium channels. Therefore, there is no reason for one of skilled in the art to conclude, *a priori*, that the $5HT_{2C}$ receptor antagonists disclosed by Gaster would function to open KCNQ channels. $5HT_{2C}$ receptors belong to the class A or rhodopsin-like G-protein-coupled receptors (GPCRs), a seven-transmembrane domain protein family. In response to ligand binding, GPCRs activate heterotrimeric G-proteins and subsequently a cascade of downstream intracellular signaling mediators. In contrast, KCNQ channels do ***not*** belong to the GPCR family, but to a completely separate class of proteins. Rather, KCNQ channels are composed of KCNQ subunits that are members of the Kv superfamily of potassium channel monomers. The KCNQ subunits form tetrameric pores, allowing ions to pass in a voltage dependent manner. The ion flow is not effected by activation of heterotrimeric G-proteins, as in the case of a GPCR. Because of the divergent structure and function of $5HT_{2C}$ receptors and KCNQ channels, there is no reason to expect a $5HT_{2C}$ receptor antagonist to increase ion flow through a KCNQ potassium channel.

11. In view of the above, it is, therefore, my scientific opinion, that one of skill in the art would not believe that the compounds of Gaster necessarily and inherently increase ion flow through KCNQ potassium channels, thereby treating anxiety. Therefore, one of skill in the art would not believe that Gaster teaches or suggests the presently claimed methods. One of skill in the art would have no motivation, nor a reasonable expectation of success of using the $5HT_{2C}$ receptor antagonists of Gaster to increase ion flow through KCNQ potassium channels to treat anxiety. The present claims are therefore not obvious in view of Gaster.

Dated:_____ _____

Alan D. Wickenden